humanized antibody with respect to the parental antibody.

20. A method of making a humanized antibody comprising the step of making the antibody identified [, following the identification of an antibody] by the method of any one of claims [1,] 7[,] or 17 [-19, the manufacture of the antibody].

21. A method of making a humanized antibody comprising the step of expressing nucleic acid encoding the antibody identified [, following the identification of an antibody] by the method of any one of claims 1, 7, [or] 17, [-] or 19 [, the expression of nucleic acid encoding the antibody].

REMARKS

The claims pending in this application are claims 1 to 13, 17 and 19 to 21. Applicants have canceled claims 14 to 16 and 18, without prejudice to file divisional applications directed thereto.

The proposed amendments to the claims are purely in response to the rejections of the Final Action. No new matter has been introduced by the claim amendments. These amendments should be considered under Rule 116 because they do not introduce issues not already fully joined in this case and because they are believed to place the claims in better condition for appeal. Further, they are offered in a good faith effort to place this case in condition for allowance.

I. Amendments

The specification has been amended to correct obvious typographical errors. With respect to the amendment to Table 1 on page 87, a copy of Carter *et al., Proc. Natl. Acad. Sci.*, **89,** (1992) is attached, which is a publication of the experimental data disclosed in the above application, and was published after the filing date thereof. It is clear that the

last two column headings of Table 1 were inadvertently superimposed and the amendment to the specification serves merely to correct these errors. It would have been obvious from the information provided on page 87 of the specification, that the last two headings were intended to be "Kd nM", and "Relative cell proliferation", respectively, as the key under Table 1 discloses what the headings indicated by † and ‡ are. Also, it is clear that the figures in the last two columns of the first line of data in Table 1 were intended to be 25 and 102 respectively, and were inadvertently superimposed. Applicants respectfully request that the specification be amended to correct the obvious typographical errors discussed above.

Claims 1, 7, 17 and 19 have been amended to refer to the consensus human variable domain "of a human immunoglobulin subgroup", with support for the amendment found on at least page 16, lines 29-32 and page 17, line 4. Claim 17, 19, and 20 have been amended to recite a preamble and a positive step, which steps are clear from at least the original set of claims filed.

II. Rejections under 35 U.S.C. § 112, second paragraph

Most of the rejections under 35 U.S.C. § 112, second paragraph, which were raised in the earlier Office Action dated October 5, 1992 have been withdrawn. Applicants thank the Examiner for withdrawing these rejections.

The Examiner has, however, maintained some of the rejections under 35 U.S.C. § 112, second paragraph, which relate to claims 1, 3-5 and 7. The separate sets of rejections are addressed separately below.

A. The Examiner has maintained the rejection of claim 1 with respect to the phrase "consensus human variable domain" because it is allegedly not clear whether the consensus domain is a culmination of different variable domains or a single universal variable domain which is homologous to other human variable domains.

In the interests of expediting examination, claims 1, 7, 17 and 19 have been amended to recite that the consensus human variable domain is "of a human

immunoglobulin subgroup". Information concerning the amino acid sequences of the *variable* domains of antibodies belonging to various human immunoglobulin subgroups was compiled by Kabat *et al., Sequences of Proteins of Immunological Interest,* Fourth Edition, U.S. Dept. of Health & Human Services, pubs., (1987), a copy of which is attached to the enclosed Kelley Declaration as Exhibit "B". Kabat *et al.* grouped various heavy and light chain variable domains according to their amino acid sequence identity to form several human immunoglobulin "subgroups" i.e. human kappa light chains subgroups I to IV, human lambda light chains subgroups I to VI and human heavy chains subgroups I to III (see pages 41-76 and 160-167 of Kabat *et al.*). The "occurrences of most common amino acids" at each position of the variable domain are provided in the second to last column for each immunoglobulin subgroup in Kabat *et al.* The consensus human variable domain claimed in the above application is an amino acid sequence comprising the most commonly occurring amino acid residues at each position of the variable domain for a particular human immunoglobulin subgroup as defined by Kabat *et al.* It would have been readily apparent, to the ordinarily skilled biochemist, what constitutes a consensus human variable domain of a human immunoglobulin subgroup upon reading the above application.

Applicants respectfully request the withdrawal of the rejection of claim 1 as indefinite in light of the above submissions.

B. The Examiner has suggested that the "import amino acid" be described as "an import antibody comprising the amino acid sequence of a non-human antibody which binds to ...". Applicants understand that the Examiner considers that inclusion of the wording "import antibody" in parentheses is unclear and that the rejection relates to claims 1, 3, 4, 5 and 7. In order to overcome the rejection, claims 1, 7 and 19 have been amended to recite "an import antibody comprising a non-human antibody...". The non-human, import antibody may be the muMAb4D5 disclosed in Example 1 of the application, for example. Claims 3-5 depend on claim 1 and because there is clear antecedence basis for the phrases "import antibody variable domain amino acid

sequence", "import sequence" and "import antibody" in claim 1, the rejection of these claims is also rendered moot.

C. The Examiner has maintained the rejection of claim 1 under 35 U.S.C. §112, second paragraph, with respect to the wording "reasonably expected" on the grounds that it is not known what criteria determines what is "reasonable". In order to obviate the rejection, Applicants have deleted the word "reasonably" from claims 1, 3 and 19. Applicants respectfully submit that the amendment to the claims renders the rejection moot.

Applicants respectfully request that the maintained rejections of claims 1, 3-5 and 7 under 35 U.S.C. § 112, second paragraph, be withdrawn in light of the amendments to the claims and the submissions under paragraphs A to C above.

III. Objection and Rejections under 35 U.S.C. § 112, first paragraph

The Examiner has maintained the objection to the specification and the rejection of claims 1 to 11 under 35 U.S.C. § 112, first paragraph as lacking enablement. New claims 17 to 21 have also been rejected under 35 U.S.C. § 112, first paragraph as lacking enablement. The various sets of rejections are addressed separately below.

A. The Examiner has maintained the rejection of claim 1 and has rejected claims 19 to 21 for including the language "at least a portion". In the interests of expediting examination, claims 1, 7 and 19 have been amended by deleting the wording "at least a portion of" therefrom. Applicants submit that the amendment of the claims renders the rejection of claims 1 and 19-20 under 35 U.S.C. § 112, first paragraph, moot and respectfully request the withdrawal thereof.

B. The Examiner has maintained the rejection that step c) of claim 1 (i.e. the step of substituting an import CDR amino acid sequence for the corresponding human CDR amino acid sequence) is not enabled by the specification. The Examiner asserts that there is no clear guidance in the specification to enable one of ordinary skill in the art to make the human "consensus variable domain". The Examiner further asserts that the

only guidance presented in the specification with regards to the substitutions is the amino acid sequences of SEQ ID NO: 3 and 4. Applicants understand that the basis for the Examiner's rejection is that the information provided in the specification would not have enabled the ordinarily skilled biochemist to carry out the methods claimed in order to produce a humanized antibody.

Applicants respectfully traverse this rejection on the grounds that the specification is enabling for the method claimed. In support of the above position, a Declaration pursuant to 37 C.F.R. § 1.132 by Robert Kelley is attached. See specifically his opinion in paragraph 3 and the bases for this opinion set forth in paragraphs 4 to 7.

This Declaration was not earlier submitted because it was believed, in good faith, that the rejection would be overcome without the need for a Declaration. Applicants respectfully request the entry of this Declaration in the above application pursuant to Rule 116, because it does not introduce issues not already fully joined in this case. The Declaration is offered in a good faith effort to place this case in condition for allowance.

As discussed under section II (A) above and in paragraph 4 of the Kelley Declaration, the consensus human variable domain constitutes an amino acid sequence comprising the most commonly occurring amino acids at each position in the variable domain of a particular human immunoglobulin subgroup as defined by Kabat *et al.* The immunoglobulin subgroups referred to in Kabat *et al.* were grouped according to the amino acid sequence homology between human immunoglobulin *variable* domains, and the most commonly occurring amino acids at each position in the variable domain for each subgroup were identified (i.e. the "consensus human variable domain"). The skilled biochemist could have used the consensus human variable domains of the light chain and heavy chain subgroups having the greatest number of sequences therein (i.e. light chains kappa subgroup I and heavy chains subgroup III) as disclosed in Kabat *et al.* (see page 17, first paragraph of the specification) to humanize the non-human antibody of interest. Alternatively, the skilled biochemist could have chosen the consensus human variable domain of another human immunoglobulin subgroup as defined in Kabat *et al.*

i.e. the consensus human variable domain for human kappa light chains subgroups II to IV, human lambda light chains subgroups I to VI, or human heavy chains subgroups I or II (see pages 41-76 and 160-167 of Kabat *et al.*). Therefore, the skilled biochemist could have elected to use a consensus human variable domain other than those defined as SEQ ID NO: 3 & 4 on page 17 of the above application, as the consensus human variable domains for other subgroups were compiled in Kabat *et al.* Page ix of Kabat *et al.* identifies the residues forming the CDR regions of heavy and light chain variable domains tabulated from human and mouse variable domains. Kabat *et al.* have adopted standardized numbering for each of the residue locations. Accordingly, the skilled biochemist could have identified the CDR regions of the consensus human variable domain and the import variable domain using the teachings of Kabat *et al.* Alternatively, the structural definition of Chothia *et al., J. Mol. Biol.*, **196:** 901-917 (1987) (see page 16, third paragraph of the specification) could have been adopted to identify the CDR regions of the consensus and import variable domains. See paragraph 4 of the Kelley Declaration. The above submissions show that steps a & b of claim 1 were enabled by the specification as filed.

Also, step c of claim 1 could have been carried out by the ordinarily skilled biochemist using the information provided in the specification and techniques such as manual tabulation of amino acid sequences or a computer program which was known in the art prior to June 14, 1991. See paragraph 5 of the Kelley Declaration.

Steps d to g of claim 1 would similarly have been straightforward to perform. These steps of claim 1 relate to the identification of Framework Region (FR) residues in the consensus human variable domain which are non-homologous to the corresponding import FR residues and replacement of such non-homologous human residues with corresponding import residues, if the residues are expected to have any one of the effects specified in step f. The locations of FR residues in human and mouse variable domains are indicated in Kabat *et al.* (see page ix) and the structural definition of the FR's was available (see Chothia *et al.*) Hence, it would have been straightforward for the skilled

immunologist to identify the FR residues in the consensus human variable domain and the import sequence. Using computer programs available before June 14, 1991, the skilled biochemist would have been able to study the 3-dimensional structure of the antibody in order to establish whether a particular non-homologous import amino acid residue is likely to have one of the effects discussed in section f of claim 1. Information is provided on pages 14 to 16 of the specification which would have enabled the skilled biochemist to determine whether any non-homologous residue(s) would be expected to have the effects claimed. The techniques claimed in steps d to g of claim 1 could have been carried out routinely by a person versed in the relevant art, prior to June 14, 1991. See paragraph 6 of the Declaration.

As discussed in paragraph 7 of the Declaration, once the primary amino acid sequence of the antibody had been characterized, it would have been routine to make the protein using recombinant techniques or a peptide synthesizer, which techniques were well known in the art prior to the filing date of the above application.

Applicants conclude that, contrary to the Examiner's assertions, the ordinarily skilled biochemist would have been able to carry out the method claimed in the above application, using the information provided in the specification and techniques which were well known in the relevant art, prior to June 14, 1991.

Accordingly, Applicants request that the rejection of claim 1 under 35 U.S.C. § 112, first paragraph, be reconsidered and withdrawn in light of the above submissions and the Declaration.

C. The Examiner has maintained the rejection of claims 1 and 3, and has rejected claim 19 under 35 U.S.C. § 112, first paragraph, with respect to the wording "reasonably" therein. In order to obviate the rejection, the wording "reasonably" has been deleted from claims 1, 3 and 19.

Accordingly, Applicants request that the rejection of claims 1, 3 and 19 under 35 U.S.C. § 112, first paragraph, be withdrawn.

D. The Examiner has maintained the rejection of claims 6, 7 and 9 as lacking

enablement under 35 U.S.C. § 112, first paragraph, the Examiner's position being that the amino acids are relevant to IgG only and not to other isotypes. Applicants respectfully traverse this rejection on the basis that the immunoglobulin *sites* claimed would have been relevant with respect to antibodies, other than IgG antibodies. Applicants refer the Examiner to paragraphs 8 & 9 of the Kelley Declaration which support this position. The Examiner appears to suggest that the rejected claims cover *sequences* which would not be found in immunoglobulin isotypes, other than IgG isotypes. However, as pointed out in paragraph 9 of the Kelley Declaration, the claims refer to *positions* or *sites* of the variable domain, not specific amino acid residues. These sites relate to the position of a residue in the 3-D structure of the variable domain. Kabat *et al.* have used universal numbering for the amino acid residue locations of the variable domains for each of the immunoglobulin subgroups mentioned therein. The FR residue sites indicated may be occupied by an amino acid residue which is non-homologous to the corresponding consensus human variable domain residue, and which residue is likely to have at least one of the effects discussed in step f of claim 1. The residue at the particular site can be any amino acid residue, depending on the antibody in which it is located. These residue locations or sites are applicable *across species* (see page 16, line 8). Accordingly, it is likely that an amino acid residue located at one of the sites indicated in claims 6, 7 and 9 will have one of the effects of claim 1 (step f) regardless of the antibody in which it is located. It is apparent that the particular sites claimed are applicable to immunoglobulins other than IgG.

Accordingly, Applicants submit that the rejection of claims 6, 7 & 9 under 35 U.S.C. § 112, first paragraph, should be reconsidered and withdrawn in light of the above submissions and Declaration.

In light of the submissions presented in paragraphs A to D above, Applicants respectfully request that the objection to the specification and the rejection of claims 1-11 and 17-21 under 35 U.S.C. §112, first paragraph, be withdrawn.

Applicants thank the Examiner for withdrawing the rejections which were raised

under 35 U.S.C. § 101 in the earlier Office Action dated October 5, 1992 .

IV. Rejection of claims 1, 2 and 5-10 under 35 U.S.C. 102 (a) and 102(b)

The rejection of claims 1, 2 and 5-10 under 35 U.S.C. § 102(a) and 102(b) has been maintained and newly added claims 17-21 have been rejected under 35 U.S.C. § 102(a) and 102(b) as being anticipated by Queen *et al., Proc. Natl. Acad. Sci.*, **86:**10029-10033 (1989) and Co *et al., Proc. Natl. Acad. Sci.*, **88:**2869-2873 (1991). The basis for the rejection is that there is allegedly no clear indication as to what is meant by the consensus human variable domain claimed in the above application.

To constitute anticipation, all material elements of a claim must be found in one prior art source. *In re Marshall*, 198 USPQ 344 (CCPA 1978), *In re Kalm*, 154 USPQ 10 (CCPA 1967). Applicants will show that Queen *et al.* and Co *et al.* do not contain all material elements of claims 1, 2, 5-10 and 17-21.

The nature of the "consensus human variable domain of a human immunoglobulin subgroup" as defined in the claims as amended has been discussed above under Section II(A) of this response and in paragraph 4 of the Kelley Declaration, those discussions being incorporated herein. Applicants submit that the meaning of the phrase consensus human variable domain of a human immunoglobulin subgroup would have been clearly understood by those skilled in the art upon reading the specification. The prior art relied upon in the Office Action fails to disclose a method of making a humanized antibody using a consensus human variable domain to "humanize" a non-human antibody. The Declaration by Kelley supports this position. In particular, Applicants direct the Office's attention to paragraphs 11-13 of the attached Declaration. It is apparent from the information given in Table 1 of Exhibit C and in the Figures of Exhibits D and E of the Kelley Declaration (see paragraphs 12 & 13 thereof), that the variable domains of the human immunoglobulin sequences used by Queen *et al.* and Co *et al.* are not a consensus human variable domain of any human immunoglobulin subgroup as set forth in the claims of the above application.

Since, as shown above, Queen *et al.* and Co *et al.* do not teach all the material elements of the instant claims as required under *Marshall* and *Kalm, supra,* Applicants respectfully submit that the rejection of claims 1, 2, 5-10 and 17-21 under 35 U.S.C. § 102(a) and (b) can not be upheld and therefore request that the rejections be withdrawn.

V. Rejection of claims 3 and 4 under 35 U.S.C. § 103

The rejection of claims 3 and 4 as unpatentable under 35 U.S.C. § 103 over Queen *et al.* or Co *et al., supra,* in view of Wallick *et al., J. Exp. Med.,* **168** (1988) has been maintained. The basis for the rejection relates to the alleged lack of clarity of the language "consensus human variable domain" in the claims of the above application. The consensus human variable domain as defined in the above application would have been readily understood by the ordinarily skilled biochemist (see paragraph 4 of the Kelley Declaration). Claim 1 of the above application relates to a method of using a consensus human variable domain to "humanize" a non-human antibody (e.g. muMAb4D5). As established in section IV above, use of a consensus human variable domain from a human immunoglobulin subgroup is not disclosed in Queen *et al.* or Co *et al.*

The publication by Wallick *et al.* does not compensate for the deficiencies in the primary references. Wallick *et al.* refer to the importance of glycosylation for maintaining antigen binding affinity of monoclonal antibodies. Wallick *et al.* fail to disclose or suggest a method of humanizing a non-human antibody, much less a method of humanizing a non-human antibody using a consensus human variable domain of a immunoglobulin subgroup. The skilled biochemist would have had no motivation to use a consensus human variable domain based on the prior art referred to in the Office Action, because the prior art techniques had all relied upon using a human variable domain sequence which has the closest sequence homology to the non-human variable sequence (to be humanized) in order to reduce the likelihood of introducing distortions into the CDR's (see column 2 on page 10031 of Queen *et al.*) and "to retain high binding affinity in the humanized antibody" (see column 1 on page 2871 of Co *et al.*). The method claimed in

the above application does not rely on a high degree of homology between the variable domain of the non-human sequence and the consensus variable domain which is used to humanize the non-human sequence.

Also, as supported by paragraph 15 of the Kelley Declaration, the invention claimed in the above application resulted in an unexpected result which could not have been reasonably predicted from the prior art. It was surprising that a consensus variable domain of a selected immunoglobulin subgroup could be used to humanize a non-human antibody, regardless of the degree of homology between the human and non-human amino acid sequences. It was also surprising that the humanized antibody so formed retained, and in some instances, had increased antigen binding affinity compared to the non-human antibody from which it was derived. The above application shows that the huMAb4D5-8 variant actually binds the $p185^{HER2}$ ECD 3-fold more tightly than muMAb4D5 (see page 82 lines 31 & 32 to page 83, line 1 of the specification) which could not have been predicted by the ordinarily skilled biochemist. See paragraph 15 of the Kelley Declaration. The evidence of unexpected results in Applicants' application is sufficient to support a conclusion of nonobviousness. *Ralston Purina Co. Far-Mar-Co., Inc.*, 222 USPQ 863 (DC KS, 1984).

It is apparent that the invention claimed in claim 1 was novel and nonobvious over the citations because the combination of the prior art failed to disclose, or suggest, the invention claimed in claim 1 and, moreover, the method resulted in a new and unexpected result which could not have been reasonably predicted from the art.

Claims 3 & 4 depend on claim 1 which, as established above, is novel and nonobvious over the citations. Claim 3 refers to the step of finding any glycosylation site which is likely to affect the antigen binding or affinity in the import antibody and substituting the glycosylation site *into* the *consensus* amino acid sequence. Claim 4 refers to the step of *replacing* glycosylation sites of the consensus domain with the corresponding import amino acid residues if such glycosylation sites are not present in the import sequence. These claims would not have been obvious over the prior art of

record because the prior art failed to disclose the use of a human consensus variable domain to humanize the non-human antibody. Accordingly, the skilled biochemist would have had no motivation to replace or insert glycosylation sites into a consensus amino acid sequence, as claimed in claims 3 and 4 of the application. See paragraph 15 of the Kelley Declaration.

The law is clear that obviousness cannot be established by combining the teachings of the references to produce the claimed invention, absent some teaching, suggestion, or incentive supporting the combination. *ACS Hospital Systems, Inc. v. Montefiore Hospital*, 221 USPQ 929, 933 (Fed. Cir. 1984). The above discussion shows that the cited references, alone or in combination, lack the requisite teaching of the use of a consensus human variable domain to humanize a non-human antibody. In this case, the combined art would not have reasonably enabled or motivated the skilled practitioner to use a human consensus variable domain in this manner, which provides a method of making improved humanized antibodies. Accordingly, it is clear that the invention claimed in claims 3 & 4 is novel and nonobvious over the prior art of record.

Applicants submit that the rejection of claims 3 and 4 under 35 U.S.C. § 103 should be reconsidered and withdrawn in light of the above submissions and the Declaration.

VI. Rejection of claims 17,18, 20 and 21 under 35 U.S.C. §112, second paragraph.

Claims 17, 18, 20 and 21 have been rejected under 35 U.S.C. § 112, second paragraph, as being indefinite in that there are allegedly no discrete method steps. In order to obviate the rejection, claims 17, 20 and 21 have been amended to each recite a definite method step and claim 18 has been deleted.

Applicants respectfully request the withdrawal of the rejection of claims 17, 20, and 21 under 35 U.S.C. § 112, second paragraph, in light of the amendments to the claims.

As all objections and rejections have been addressed and overcome, Applicants

believe that the claims are now in condition for allowance. Notice to that effect is respectfully requested. If the Examiner has any questions concerning the response, she should feel free to call the undersigned attorney at the number indicated above.

Respectfully submitted,
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Date: September 20, 1993

CERTIFICATE OF MAILING (37 CFR 1.8a)

I hereby certify that this paper is being deposited with the United States Postal Service on the date shown below with sufficient postage as first class mail in an envelope addressed to the: Commissioner of Patents and Trademarks, Washington, D.C. 20231.

Louise Strasbaugh

Louise Strasbaugh

Date: September 20, 1993